Amendments to the Specification:

Amend the paragraph beginning at page 31, line 23, as follows.

Fig. 2A shows the predicted *C. elegans* DAF-2 amino acid sequence (SEQ ID NO:12). The predicted cysteine-rich region (amino acids 207-372) and tyrosine kinase domain (amino acids 1124-1398) are boxed. The signal peptide (amino acids 1-20), proteolysis site (amino acids 806-809), transmembrane domain (amino acids 1062-1085), and PTB binding motif in the juxtamembrane region (NPEY, amino acids 1103-1106; SEQ ID NO:12) are underlined. Three DAF-2 tyrosine residues, Y1293, Y1296 and Y1297, in the region corresponding to the insulin receptor kinase Y1158 to Y1163 activation loop are likely to be autophosphorylated, based on the predicted similarity between the DAF-2 and insulin receptor phosphorylation targets (~~Fig. 2B~~ Fig. 2C). Another likely target for DAF-2 autophosphorylation is the Y1106 NPEY motif located in the region corresponding to the insulin receptor juxtamembrane region NPEY motif (at Y972), that has been shown to mediate IRS-1 binding via its PTB domain to the insulin receptor (White and Kahn, *J. Biol. Chem.* 269: 1-4, 1994). While DAF-2 bears one YXXM motif implicated in coupling to PI 3-kinase, mammalian IRS-1 and *Drosophila* insulin receptor (Fernandez et al., EMBO J. 14: 3373-3384, 1995) bear multiple YXXM motifs. Although no p85-like adaptor subunit has yet been detected in the *C. elegans* database, the AGE-1 homology to mammalian p110 suggests the existence of a homologous or analogous adaptor (Morris et al., *Nature*

382: 536-539, 1996). In the DAF-2 C-terminal domain, two other tyrosine residues may be autophosphorylated and bound to particular SH2-containing proteins: Y1678 binding to a PLC-g or SHP-2 homolog, and Y1686, perhaps binding to SEM-5 (Fig. 2A) (Songyang et al., *Cell* 72: 767-778, 1993). While mutations in, for example, ras and MAP kinase have not been identified in screens for dauer constitutive or dauer defective mutations, these general signaling pathway proteins may couple to DAF-2 as they couple to insulin signaling in vertebrates (White and Kahn, *J. Biol. Chem.* 269: 1-4, 1994). The predicted phosphotyrosine residues in juxtamembrane region and the kinase domain activation loop are circled. In the extended C-terminal region, predicted phosphotyrosine residues are also circled and SH2-binding sites are underlined (see below).

Amend the paragraph at page 32, line 26, as follows.

Figs. 2B-1, 2B-2, and 2B-3 show the cDNA encoding the *C. elegans* DAF-2 (SEQ ID NO:11).

Amend the paragraph beginning at page 33, line 1, as follows.

Figs. 2C-1 and 2C-2 show the amino acid comparison of *C. elegans* DAF-2 (SEQ ID NO:106) to the human insulin receptor (SEQ ID NO:104) and human

IGF-I receptor (SEQ ID NO:103) (shown in parenthesis), and to the *Drosophila* insulin receptor homolog (SEQ ID NO:105), with *daf-2* and human insulin receptor mutations highlighted. Six *daf-2* mutations map in the ligand-binding domain: *sa187* (C347S, TGT to AGT), *e1368* (S451L, TCA to TTA), *e1365* (A458T, GCT to ACT), *sa229* (D526N, GAT to AAT), and two mutations in *mg43* (C279Y, TGT to TAT and P348L, CCC to CTC). Three *daf-2* mutations substitute conserved amino acid residues in the insulin receptor kinase domain: *sa219* (D1252N, GAT to AAT), *e1391* (P1312L, CCC to CTC), and *e1370* (P1343S, CCA to TCA). Darkened residues indicate amino acid identity. Hatched residues indicate amino acid similarity. The percentages under the domains represents the percentage of identity observed between DAF-2 and each receptor. The corresponding BLAST probabilities of DAF-2 random match to each protein is: 6.4×10^{-157} (human insulin receptor), 2.7×10^{-156} (human IGF-I receptor), 2.1×10^{-153} (molluscan InR homolog), 8.3×10^{-153} (mosquito InR homolgoue), 1.6×10^{-138} (human insulin receptor-related receptor), $1.7x\ 10^{-122}$ (*Drosophila* InR homolog), 2.0×10^{-108} (Hydra InR homolog). DAF-2 is more distant from the next most closely related kinase families: 8.9×10^{-58} (v-ros) and 3.0×10^{-51} (trkC neurotrophin receptor).

Amend the paragraph beginning at page 36, line 12, as follows.

Fig. 5C shows the protein sequence alignment of *C. elegans daf-3* (SEQ ID NOS:111 and 113) and the closest homolog found to date, human DPC4 (SEQ ID NOS:112 and 114), in the Smad conserved domains I and II. Dots indicate gaps introduced to maximize alignment. DAF-3 is 55% identical to DPC4 in domain I and 30% identical in domain II. *daf-3*(mg125) and *daf-3(mg132)* mutations are indicated by boldface and underline. The Smad mutational hotspot is underlined. In addition to *mg125* and *mg132*, seven other *daf-3* alleles were sequenced in the hotspot; none of them contains a mutation. Alleles sequenced were *mg91*, *mg93*, *mg105*, *mg121*, *mg126*, *mg133* (isolated by A. Koweek and G. Patterson, unpublished) and sa205.

Amend the paragraph beginning at page 39, line 9, as follows.

Figs. 21A-1, 21A-2, and 21A-3 are illustrations showing that human FKHR and AFX are the closest relatives to DAF-16 (SEQ ID NOS: 45, 57, and 99-102). Note that the differentially spliced DAF-16 forkhead domain is less homologous.

Amend the paragraph beginning at page 39, line 22, as follows.

Fig. 25 is an illustration showing the comparison of *C. elegans* AKT (SEQ

ID NOS: 88, 90, 92, 94, 96, and 98) with mammalian AKT (SEQ ID NOS:87, 89, 91, 93, 95, and 97).